Chromosome Structure Diseases

Introduction

Structural chromosome changes require a break of the DNA. That break can result in a simple loss (**deletion**) of genetic material, or it can result in the formation of exchange. Exchange can take the form of a **translocation**, **ring**, **inversion**, or **isochromosome**. The primary emphasis of this discussion is on translocations. These discussions get in depth to leave out questions. It may appear to be more complex than most texts.

Generations and Crossovers

Crossover events that occur during meiosis affect gametes. The individual that suffers the crossover event in the formation of their gametes is **generation 1** and is **both asymptomatic** and **genetically normal**. The gametes that form can be normal or abnormal. If an abnormal gamete is used to fertilize a gamete of a healthy mate, the resulting individual in **generation 2** remains **asymptomatic** despite being **genetically altered**. Generation 2 remains asymptomatic because although there was a crossover event, the genetic complement is normal. The genes are in the wrong place, and the karyotype will be abnormal, but the genetic code that is carried is intact. Generation 2 is in the **carrier state**.

The real danger is in **generation 3**, which will be **symptomatic** and **grossly genetically defected**. The gametes that are made by that generation 2 carrier will pair with a healthy mate. But the gametes that are made by generation 2 can be either normal, or perpetuate the carrier, or be grossly abnormal so as to produce partial trisomy or partial monosomy in the offspring. Partial monosomy and partial trisomy are almost as poorly tolerated as complete monosomy or complete trisomy; they will result in fetal loss.

This generation 1 (non-carrier, asymptomatic) to generation 2 (carrier, asymptomatic) to generation 3 (disease, fetal loss) is especially poignant for translocation, with which we'll start. The generational pattern is a product of crossover events in meiosis during gametogenesis. Technically, a crossover event could occur during early mitosis of a developing zygote, which would result in the same generation 2 asymptomatic carrier state.

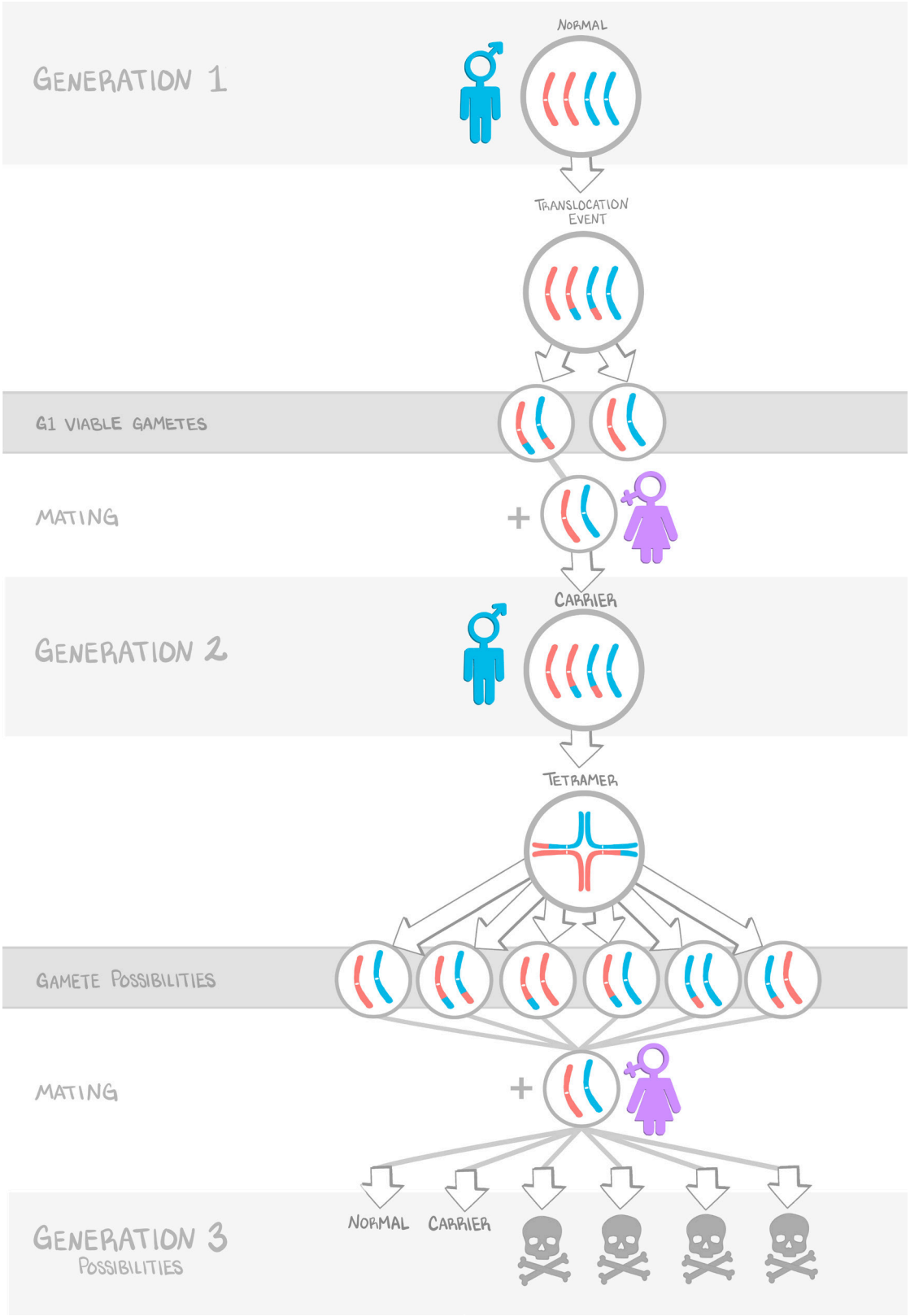

Figure 7.1: Generations
The translocation event in the formation of the gametes in generation 1 is not felt until generation 3. Generation 1 is healthy, generation 2 is an asymptomatic carrier, and generation 3 feels the effects.

A structural change is said to be **balanced** if there's no change in function, if there's a complete genetic complement, even if it's split up in ways it should not be. It's usually the result of generation 2. They're balanced because they have all their genes, but they predispose their offspring to being unbalanced because they're abnormally arranged. **Unbalanced** structural changes are where there's a **gain or loss of function.** Either is bad. Having too many alleles for one gene is bad; having not enough is bad. These patients are usually symptomatic and the product of generation 3.

Structural Lesions within Developed Organisms: Mitosis

Lesions occurring in **mitosis** will affect the somatic cell. Because a single structural lesion in a single cell amongst billions means very little to function, almost all somatic mutations are irrelevant. There could be a crossover event during mitosis of a recently fertilized egg, which would technically result in a "generation 2 individual" or "mosaicism," but this is hard enough as is. Assume that meiosis in gametes leads to generation 2 carriers and generation 3 affecteds. The only time a crossover event matters in somatic cells is when it comes to **oncogenes** and **tumor suppressors**.

Leukemia			
t9;22	BCR-ABL	CML	Imatinib
t15;17	Retinoid-receptor-α	AML	All trans-retinoic acid

Lymphoma		
t8;14	Burkitt's	Myc-c
t11;14	Mantle cell	Gain of function
Bcl-2	t14;18	Follicular

Table 7.1: Translocations and Cancer
Examples of translocations that result in either leukemia or lymphoma.

Reciprocal Translocation: How They Happen in Gametogenesis of Generation 1

A **crossover event** occurs in the **gametogenesis** of **generation 1**, the gamete that will become the generation 2 offspring. This crossover event can be between **homologous chromosomes**, in which case the genetic material is **shared equally.** This is called **recombination**; it doesn't result in genetic disorders. When this crossover event occurs between **non-homologous chromosomes,** the unbalanced, unequal exchange of genetic material promotes partial trisomy or partial monosomy in the respective gametes.

While reciprocal translocations often have little impact on the second-generation carrier (most are **asymptomatic carriers**), the variable genotype of generation 2 gametes (the gametes that will become generation 3) are highly variable. We discuss how in the next section.

Reciprocal Translocation's Consequences and How Generation 2 Forms Gametes

We're discussing generation 2. During gametogenesis of generation 1, there was a crossover event where chromosome 1 had swapped with chromosome 2. This was a balanced translocation because it gave rise

to a gamete with a complete set of genes, and the individual of generation 2 is a carrier. Now it's time for generation 2, this current individual, the person with this translocation in **all of their cells**, to make gametes. The cell is ready to enter meiosis I. During meiosis I, homologous chromosomes must pair with each other. But in this individual, two chromosomes have within them two different chromosomes (chromosome 1 has part of chromosome 2, and chromosome 2 has part of chromosome 1). The chromosomes still must line up next to each other. To do that, now **pairing four chromosomes instead of two,** a tetramer forms.

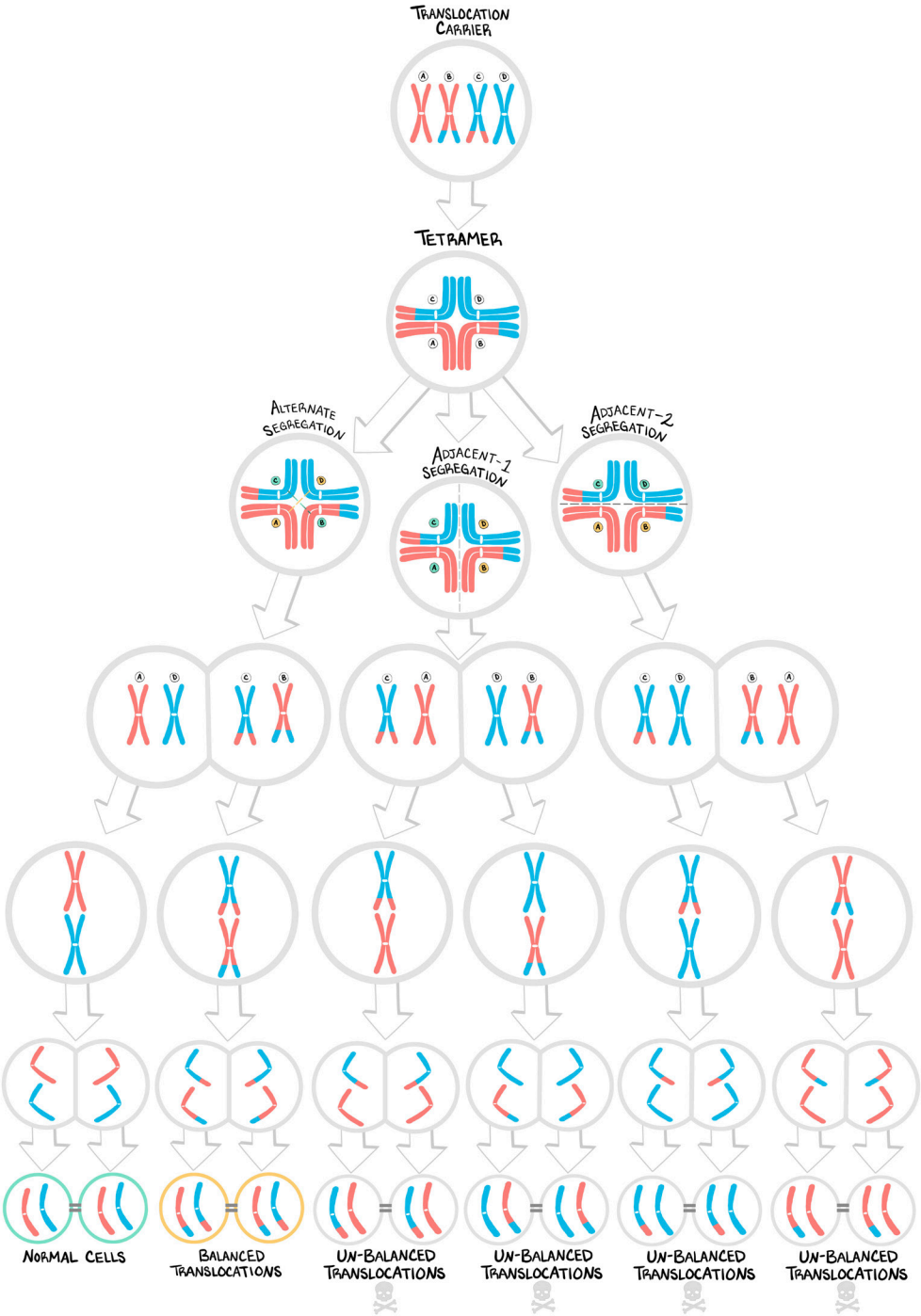

Figure 7.2: Detailed Possibilities of Gametogenesis with Translocation
This walks us through the different permutations of adjacent and alternate segregation while considering every chromatid. The punchline is that you need not worry about chromatids, only chromosomes (which simplifies the next figure).

Because this tetramer isn't oriented at the metaphase plate, there are three potential ways the microtubules can attach and begin the process of separating chromosomes from each other. If the microtubules attach such that **adjacent** pairings will be **next to each other** in the shape of the tetramer, either the original sister homologs separate together (adjacent-1) or they separate from each other with their crossover pair (adjacent-2). In a three-dimensional fashion that's a struggle to imagine, the **alternative** pairing goes **across the tetramer**. **Alternative** pairings are **across the tetramer**, 1 with 3, 2 with 4.

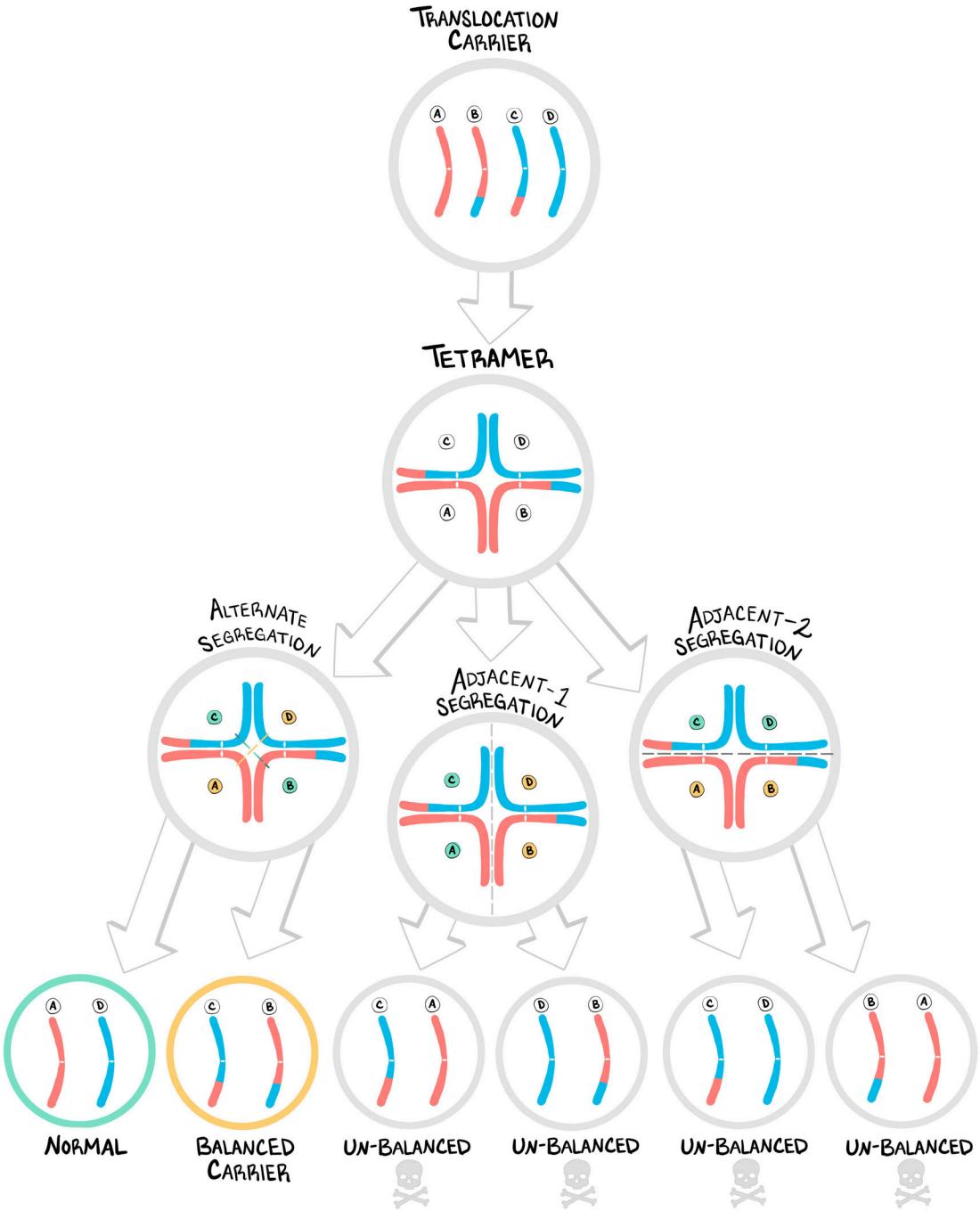

Figure 7.3: Translocation Tetramer
How they will orient, and how the mitotic spindle will see them, cannot be predicted. However, what is clear is that adjacent segregation results in an unbalanced translocation while alternative segregation results in balanced carriers or normal offspring.

Recurrence risk is high with translocations. Because the gametes made by generation 2 are more likely unbalanced (and therefore likely nonviable or at least diseased) than balanced, generation 2 will have a hard time conceiving, and those that are conceived have a higher likelihood of recurrence. Trisomy is poorly tolerated. Monosomy effectively is not tolerated at all. Now with the reciprocal forms, there's partial trisomy and partial monosomy. Neither is tolerated well, but both are better tolerated than full trisomy or monosomy. The presence of trisomy from nondisjunction occurs in the formation of that **one gamete**. And while nondisjunction is more common than translocation, nondisjunction is not likely to happen again. It's one random event in one random gamete. However, in a patient who is a carrier for translocation disease, the **predisposition for trisomy is in almost every gamete** (the unbalanced 4 to the right).

Robertsonian Translocation

Just like reciprocal translocations, the **translocation event** is in **generation 1's gametogenesis**, is carried in generation 2 as an asymptomatic carrier, and is expressed in generation 3. Robertsonian translocation is a special form of translocation that occurs between **acrocentric chromosomes.** The **two chromosomes merge**, sacrificing their short p-arms and joining their two q-arms. This is effectively the same process as reciprocal translocation, except that **two chromosomes become one**. This happens during **gametogenesis** of generation 1, leading to offspring that have a **balanced translocation.** Even though the offspring has only 45 chromosomes physically, one of those 45 chromosomes has the genetic material of 2 chromosomes.

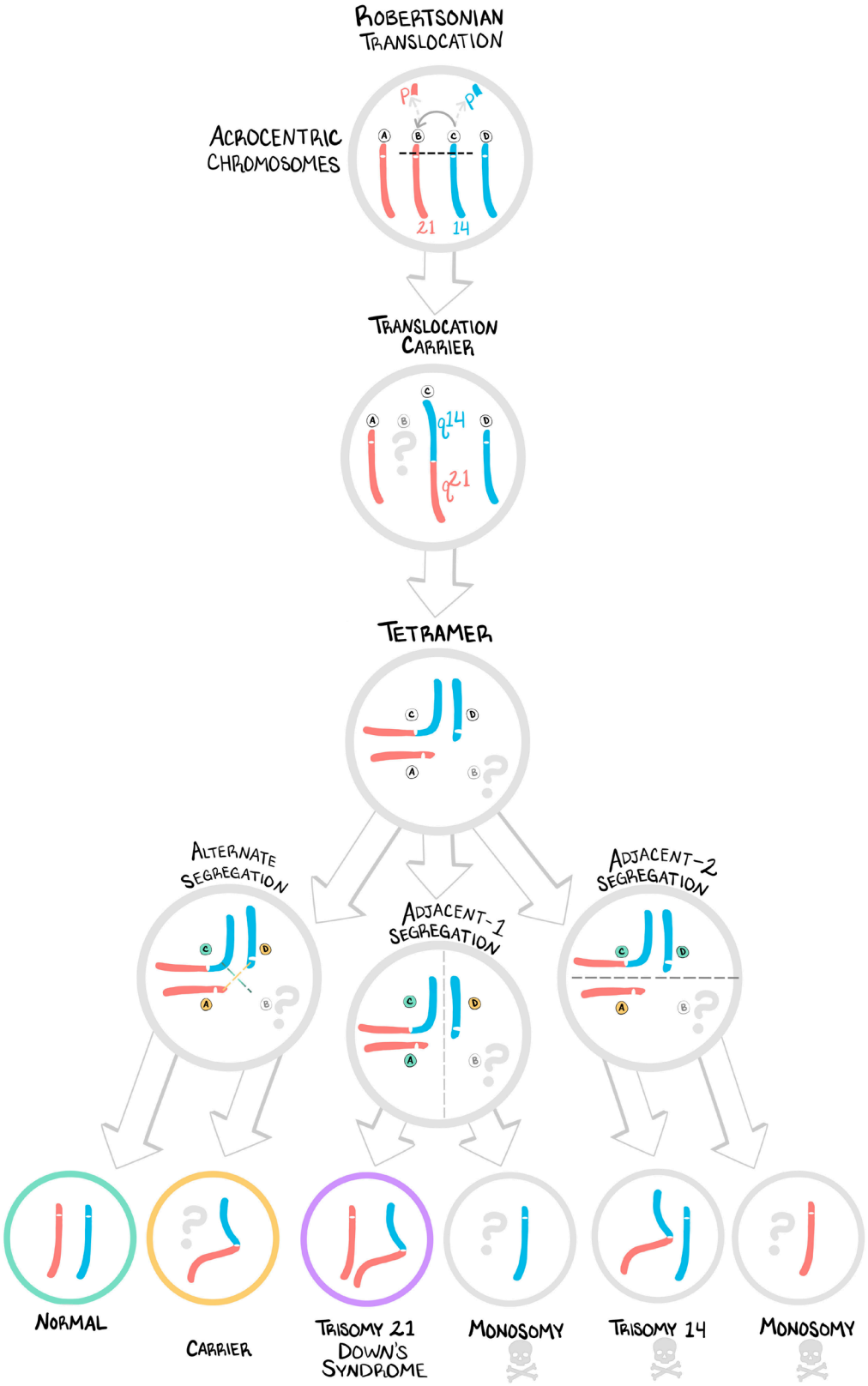

Figure 7.4: Robertsonian Translocation
Occuring only between acrocentric chromosomes, this results in a "tetramer" without any chromosome in one of the quadrants. Again, adjacent results in problems, while alternate segregation results in an asymptomatic carrier or normal offspring.

Consequences of Robertsonian Translocation

Again, just as with reciprocal translocation, we can end up with a totally normal offspring or a carrier state as a result of **alternate pairing**, and we have **partial monosomy** and **partial trisomy** as a result of **adjacent pairing**.

Down syndrome is more commonly caused by nondisjunction (95% of cases) than by Robertsonian translocation (5%). But if there's a Robertsonian translocation t14:22, then the **risk of recurrence** is substantially elevated over another nondisjunction. This is because the Robertsonian translocation is present in every attempt at gametogenesis.

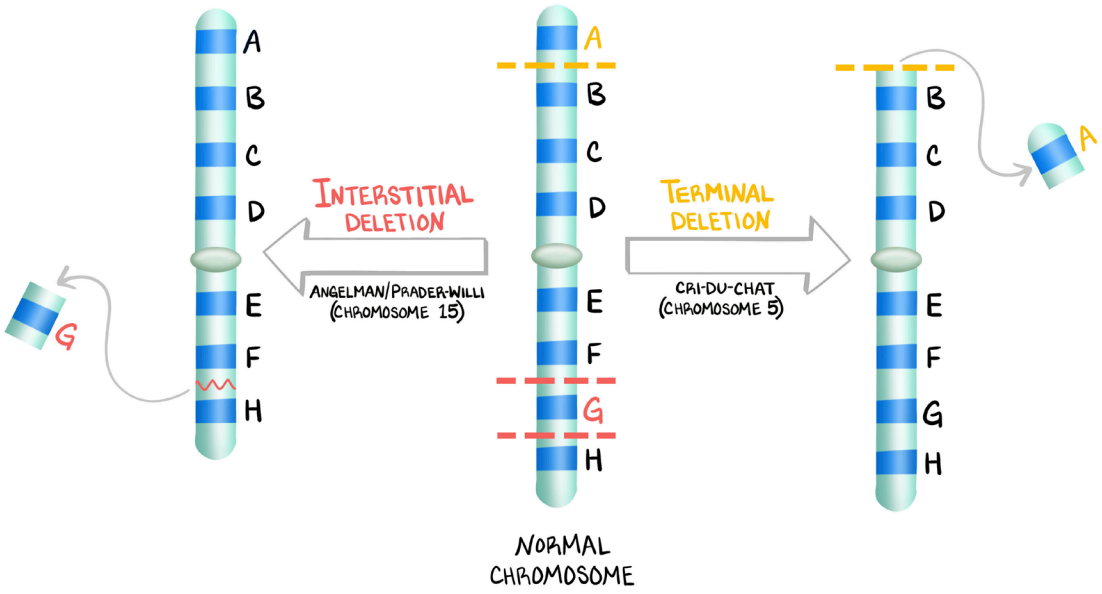

Figure 7.5: Deletion
Interstitial deletions are loss of DNA within a chromosome and require two breaks. Terminal deletions are loss of DNA fragments at the ends of chromosomes and require one break.

Deletion

If the breaks in DNA result in the loss of segments of the chromosome, we have a deletion. A **terminal deletion** is one that involves the tip of the chromosome and requires only one break in the DNA. An **interstitial deletion** is one that requires more than one break in the DNA, and removes a segment of DNA, but reattaches the separated pieces. If the deleted segment contains a gene, the gene is lost. There can be both gain of function (loss of a stop codon) or a loss of function (removal of coding sequence), though most often there is no change in function, only spacer DNA having been lost.

Cri-du-chat (French for "cry of the cat") is an example of a terminal deletion on the **short arm of terminal 5**. It's rare, and is characterized by the sound the child makes, which sounds like a cat crying. It also shares many features with live partial trisomy or partial monosomy: **small head/jaw**, **intellectual disability**, and a **syndromic face**.

Angelman syndrome and **Prader-Willi** are better used to demonstrate methylation and inactivation of genes. Males inactivate one portion of chromosome 15 and females another. When there's an **interstitial deletion of chromosome 15** and the un-methylated, active copy is lost, the present copy—the one methylated and inactivated—can't account for the absent deleted version. If there's Angelman syndrome, then the child has the father's gene (inactivated chr 15q13) and the deletion was in the mother's active

copy. If there's Prader-Willi, then the child has the mother's gene (inactivated chr 15q11) and the father's active copy was deleted.

Prader-Willi is characterized by intellectual disability, small hands and feet, weakness of all muscles, the inability to stop eating, and gross obesity. Angelman, called happy-puppet syndrome, is characterized by stiff, jerky movements (like a marionette) as well as seizures. Syndromic features are present as well, such as small head and flatness in the back of the head.

Inversion

Inversion occurs when there are two breaks in the DNA of a chromosome, and that chromosomal segment is flipped around and reconnected to the same chromosome. If the inversion **includes the centromere**, it's called **pericentric**; if it doesn't, it's called **paracentric**. This causes **no loss of DNA content** and retains the 46 chromosomes without any partial monosomy or partial trisomy. Unless the break is inside a coding segment of a gene, inversions often do **very little, symptomatically**. However, they do **substantially increase the risk of translocation**.

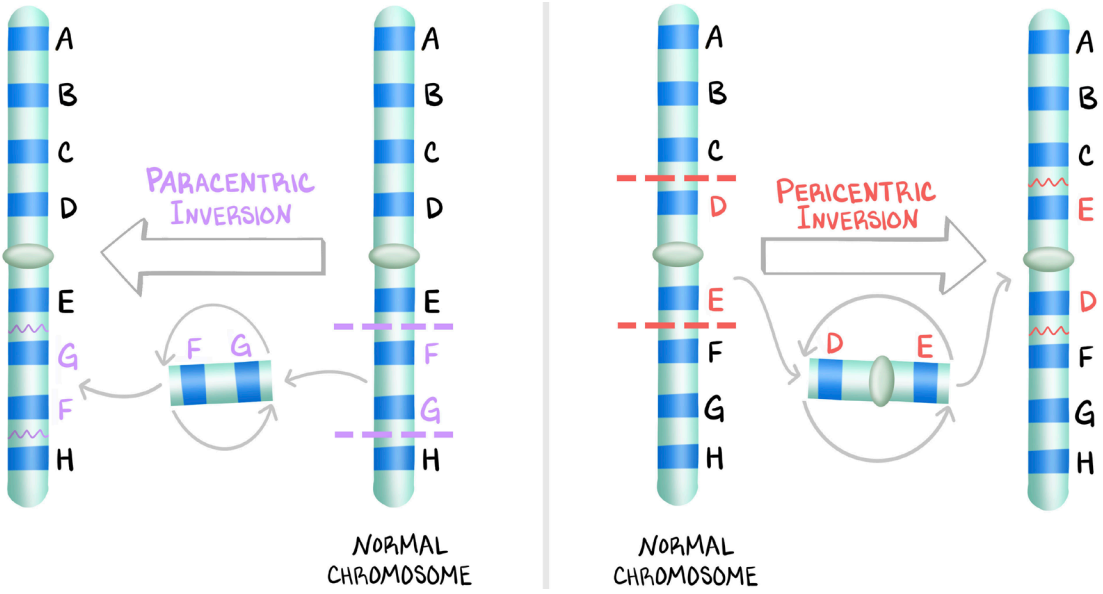

Figure 7.6: Inversion
If two breaks are made and the DNA leaves, it's a deletion. If the DNA simply flips around and reattaches, it's an inversion. Involvement of the centromere means it's pericentric, otherwise it's paracentric.

Ring Chromosome

If the DNA breaks at the ends of the chromosome, it can attach its two ends together to form a ring. Rings cannot pair with their homologous sister chromosome and are often lost, resulting in potential **monosomy**. Cells with entire chromosomes deleted usually die. Gametes made with a monosomy will not produce a viable zygote. Humans cannot tolerate a monosomy of any chromosome except sex chromosomes.

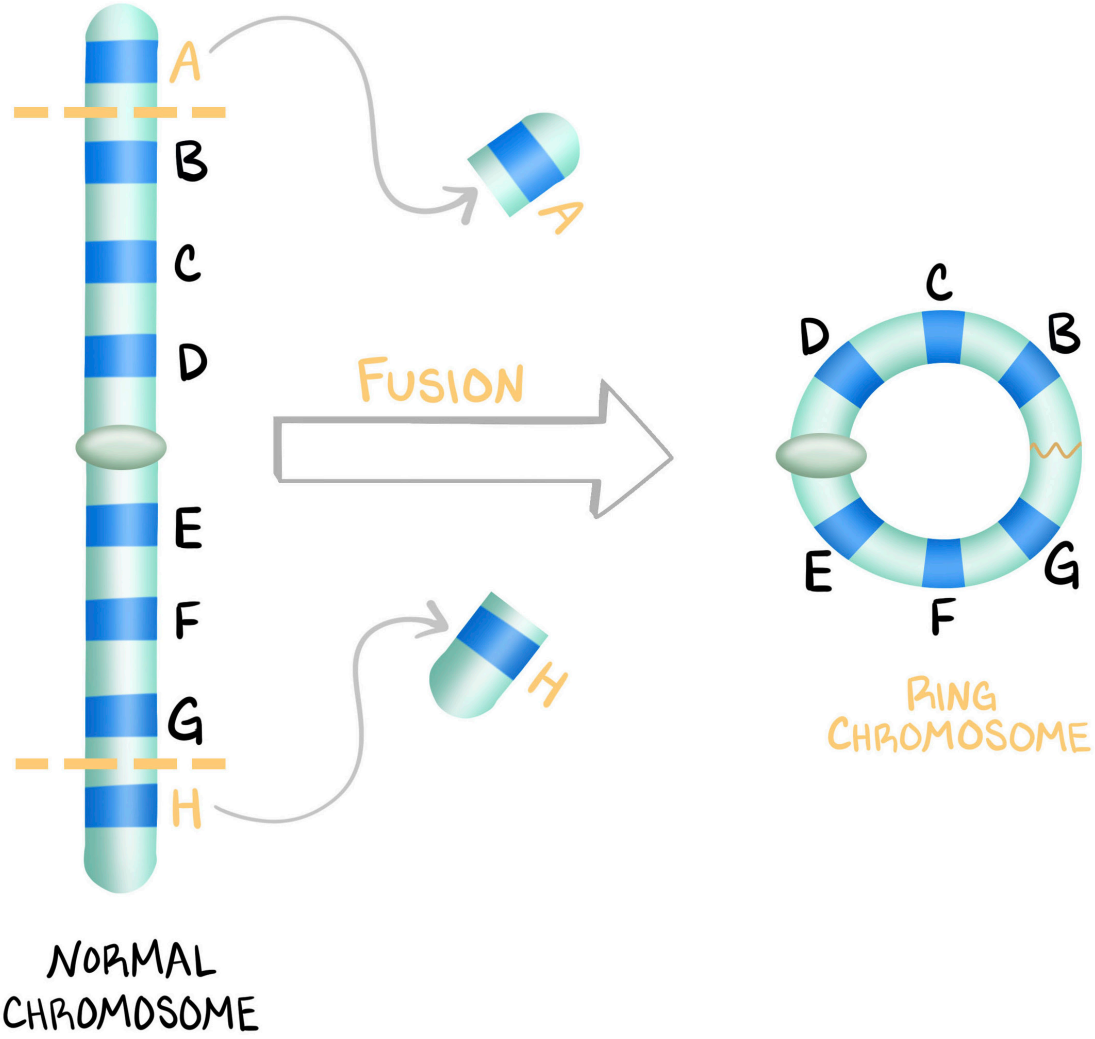

Figure 7.7: Ring Chromosome
Two breaks at the distal end of a chromosome can result in the formation of a ring. Ring chromosomes cannot pair with their homolog, and are often lost.

Isochromosomes

An isochromsome is sort of an auto-Robertsonian-translocation. The q-arm of one chromosome takes the place of the p-arm of another chromosome. This reduces the chromosome complement by one (it's a monosomy), but doesn't compromise the genetic material as substantially—there are still two copies of the q-arm, just no copies of the p-arm. **Autosomal isochromosomes are lethal**, so the only instance could be the sex chromosome. The normal chromosome is X, the isochromosome is iXq. This condition causes Turner syndrome, which is typically discussed as missing an X chromosome.

X has both the p- and the q-arm. iXq has only q-arms. Barr bodies form in these patients. If the X chromosome inactivates and becomes the Barr body, only the iXq remains. Since these patients develop Turner's, therefore, we deduce that the genes required to prevent Turner syndrome are on the p-arm of the X chromosome. This form of Turner is 270+ land and is written 46,X,i(Xq).

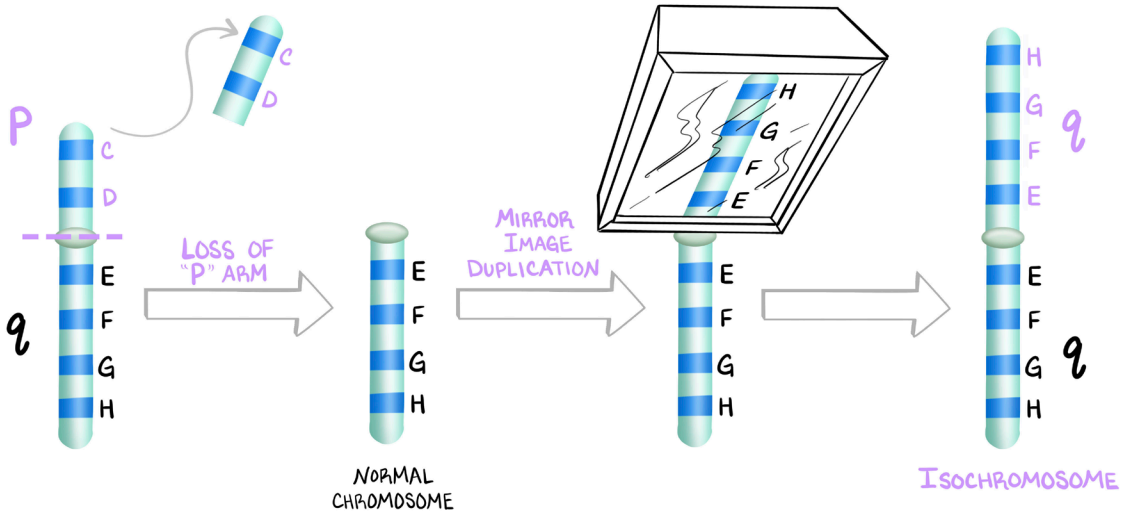

Figure 7.8: Isochromosome
Loss of the p-arm results in duplciation of the q-arm, resulting in a double-q chromosome.